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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1805	11

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Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.	Applicant(s)
08/467,397	Frank et al.
Examiner	**Group Art Unit**
Bonnie Weiss	1805

☒ Responsive to communication(s) filed on *Sep 25, 1996* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-224* is/are pending in the application.

Of the above, claim(s) *52-206* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-51 and 207-224* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

This Action is responsive to the amendment filed 9/25/96 (Paper No. 10), wherein claims 1, 17 and 19 were amended and new claims 207-224 were added. Please note that, although the "Remarks" section of the amendment states that nonelected claims 51-206 have been cancelled, these claims, in fact, have not been formally cancelled and are still pending. However, claims 51-206 remain withdrawn from consideration as being drawn to a nonelected invention.

The rejection of claims 1, 40-45, 48 and 50 under 35 U.S.C. 102(b) is withdrawn in view of applicants' amendment to claim 1 in Paper No. 10.

1. Amended claims 17 and 19, and new claims 211-213, 215-222 and 224 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over either Wu et al. (IDS, B4) or Wu et al. (93/04701-A1) for reasons made of record in Paper No. 8.

Applicant's arguments filed in Paper No. 10 have been fully considered but they are not deemed to be persuasive.

Applicants have amended the claims 17 and 19 to specifically state that the instant oligos are complementary to a portion of the HBV RNA, arguing that such oligos are not anticipitated by the oligo of Wu et al., presumably since that oligo was designed

to be complementary to part of the HBV genome. However, an oligo complementary to the sense strand of the genome would have the same nucleotide sequence as an oligo complementary to the RNA. Furthermore, as stated previously and as shown in the PCT, page 12, line 1, the specific sequence of the Wu oligo encompasses those of applicants' HBV101 and HBV71.

In an analysis to be expanded on below, contrary to the applicants' assertion in Paper No. 10, the references submitted as Exhibits A through D do not teach away from obviousness. Regarding the rejection of the above claims under Wu et al., it is noted in Ecker et al. (Exhibit C, part I) on page 1855, column 1, last sentence, that "shorter pharmacophores" (oligos having pharmaceutical potential) may be identified within longer sequences by determining which nucleotides are essential for activity. Thus, rather than teaching away from the Wu et al. references, Ecker et al. supports the contention that it would, at the very least, be obvious to take an oligo known to exhibit antisense inhibition, such as that taught by Wu et al., and derive a shorter version(s) by identifying the essential nucleotides.

Applicants' efforts to keep the record complete by pointing out that the oligonucleotide of claim 18 (SEQ ID NO:17) would also be encompassed by that of Wu et al. are appreciated (page 7, last paragraph). However, this was not found to be the case since the oligo of Wu et al. corresponds to nucleotides 1903-1923

of HBV and the oligo of claim 18 corresponds to nucleotides 1903-1929.

2. Claims 1, 18, 20, 40-45, 48 and 50 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al., cited above, in view of Ono et al. for reasons made of record in Paper No. 8.

Applicant's arguments filed in Paper No. 10 have been fully considered but they are not deemed to be persuasive.

Applicants argue on page 8 of Paper No. 10 that the oligo of Wu et al. and the disclosure of the entire HBV genomic sequence given in Ono et al., do not, in combination, render obvious oligos having sequences that overlap that of Wu et al. For support, as mentioned above, applicants have submitted several references which reveal studies in which the addition or deletion of a few nucleotides to an oligonucleotide can abolish its antisense activity.

However, the results communicated in Exhibits A-D are clearly biased by potential secondary structures of the target mRNAs. For instance, Westermann et al., who attempt to inhibit SV40 virus replication using antisense oligonucleotides conjugated to polylysine, specifically state on page 92 in the first full paragraph that oligo E would not be expected to work due to known secondary structure involving the complementary region of the viral mRNA. Also, although a low level of inhibition for several of the other oligos was reported in Table

1, Westermann et al. report at the bottom of page 90 that repeated addition of the oligo conjugates increased the inhibitory activity (as reported in Table 2), suggesting that the regiment of treating cell monolayers needed only to be optimized.

Similarly, Lima et al. state on page 12060, column 1, that the binding of the antisense oligos to the Ha-ras transcript was greatly influenced by the secondary structure of the associated stem-loop formation (also see the abstract).

Daibata et al. teach the use of three overlapping antisense oligos for the inhibition of EBV replication, and report that while oligos Z-1 and Z-3 mediated inhibition, oligo Z-2 was not as effective. Although Daibata et al. do not speculate on the reasons for the reduced activity of the Z-2 oligo, the relative GC content of the three oligos is quite different and could very well be the reason for the varying degrees of inhibition. Oligo Z-2 contains 35% GC, while oligos Z-1 and Z-3 contain 44% and 50%, respectively. One of ordinary skill in the art is aware of the importance of GC content, particularly in the art of antisense inhibition, and would have known to examine "overlapping" oligos for a specific target displaying a range of GC contents to determine the appropriate balance between oligo strength and specificity.

Lastly, although the antisense inhibition of HIV expression reported by Matsukara et al. appears to be sequence specific for reasons that are unknown to the authors, it is also clear that

the results reported by Matsukara et al. were unexpected in light of other reports in the art. For instance, Matsukara et al. state on page 4247, column 2, lines 5-8, that it has not previously been possible to demonstrate sequence specificity or dose-response relationships for antisense inhibition of HIV.

Contrary to what has been experienced in the art regarding antisense inhibition of HIV, HBV has been an amenable target for antisense inhibtion, as set forth in Paper No. 8. Furthermore, applicants have not pointed out any potential secondary structures of HBV mRNA that would render the results of the instant application unexpected. Without a showing that inhibition of HBV relication would have been unexpected with the oligos disclosed in the specification, the oligos and the use thereof to mediate antisense inhibition are obvious in view of Wu et al. and Ono et al. as originally set forth in Paper No. 8.

3. Claims 46 and 47, and newly submitted claims 213, 214, 221 and 223, are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. in view of Uhlmann et al.

Claim 46 is drawn to the oligo of Claim 44 (which contains at least one deoxyribonucleotide as described above), further comprising at least one ribonucleotide. Claim 47 is drawn to the oligonucleotide of Claim 45 (which contains at least one ribonucleotide as described above), further comprising at least one 2'-O-methyl nucleotide. The newly submitted claims above

recite the same embodiments but are inherently directed to amended claims 17 and 19, respectively.

As stated in Paper No. 8, Wu et al. teaches HBV oligos that may be either DNA or RNA. Wu et al. does not specifically teach an oligo containing both DNA and RNA, nor an oligo containing a 2'-O-methyl nucleotide.

Uhlmann et al. discuss chimeric RNA/DNA oligonucleotides on page 573, column 1, lines 9-12, as a means of creating site-specific cleavages in a target molecule using RNase H.

Uhlmann et al., on page 558, column 1, section 2, discuss 2'-O-methyl oligoribonucleotide derivatives and the use of such a modification to increase the stability of oligoribonucleotides.

Since applicants only arguments concern the obviousness of an oligonucleotide that overlaps, encompasses or is included within the nucleotide sequence of another proven to have antisense activity, and this argument has been addressed above, a *prima facie* case of obviousness remains. It would have been *prima facie* obvious to one of ordinary skill in the art to modify the oligos taught by Wu et al. with the modifications taught by Uhlmann et al. for the purpose of generating site-specific cleavages in HBV RNA and increasing the stability of the HBV-directed oligonucleotides.

4. Claims 1-9, 33-35 and 37-39 remain rejected under 35 U.S.C. § 103 as being unpatentable over Oh et al. in view of Ono et al. for reasons made of record in Paper No. 8.

Oh et al. teach the use of antisense oligonucleotides complementary to the S, X, and P genes of HBV (the abstract). The oligos used by Oh et al. are not identical to the oligos of the instant application.

Ono et al. teach the entire sequence of the HBV genome and define the boundaries of the HBV genes.

Since applicants only arguments concern the obviousness of an oligonucleotide that overlaps, encompasses or is included within the nucleotide sequence of another proven to have antisense activity, and this argument has been addressed above, a *prima facie* case of obviousness remains. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the oligos taught by Oh et al. inhibited HBV replication (see the abstract), to use the sequence taught by Ono et al. to design other oligos that were complementary to portions of either the X or P gene for the purpose of inhibiting HBV replication.

5. Claims 1-4, 15-35, 37-39, 44, 50, and 51, and new claims 207-212, 215-220, 222 and 224, are rejected under 35 U.S.C. § 103 as being unpatentable over Offensberger et al. in view of Ono et al. for reasons made of record in Paper No. 8.

Applicants state in the specification, page 4, lines 15-20, that the oligonucleotides designed by Offensberger et al. were directed to the 5' region of the pre-S gene and were shown to inhibit replication of duck HBV *in vivo*. This is supported in the abstract of the reference. However, other oligos were also tested by Offensberger et al. as depicted in Figure 1 and described on page 1257, column 2, lines 24-30. One oligonucleotide, AS 5, was directed to the start of the polymerase region and four oligonucleotides, AS 6-9, were directed to the preC/C region. All oligonucleotides led to a decrease of intracellular viral intermediates, although AS 2 (directed to the preS region) and 6 (directed to the preC region) were described as the most effective (page 1257, column 2, lines 38-49). In addition, it is well known in the art, as depicted in both Figure 1 of the reference and Figure 1 of the instant specification, that the genes of HBV overlap eachother on the genome. Thus, an oligo directed toward the start of the P region that is effective at inhibiting HBV replication would also suggest that an oligo directed toward the C region would also be effective since the P region begins within the C region.

Offensberger teach oligos that are complementary to duck HBV and do not teach oligos that are complementary to human HBV. However, Ono et al. teach the entire sequence of the HBV genome and define the boundaries of the HBV genes.

Applicants argue on page 14 of Paper No. 10 that oligonucleotides directed to the HBV genome of another species are not necessarily predictive of the specific nucleotides set forth in applicants' claims, and argue again that minor changes in position and length may greatly influence antisense activity. Absent some showing that human HBV mRNA would form a potential secondary structure that duck HBV mRNA does not, or arguments discussing important differences in the life cycles of human and duck HBV, a *prima facie* case of obviousness is maintained. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the oligos taught by Offensberger et al. inhibited HBV replication in ducks, to target the regions taught by Offensberger et al. by designing oligos that are complementary to the equivalent regions of human HBV for the purpose of inhibiting HBV replication in humans.

6. Claims 1-9, 14-18, 33-35 and 37-44, and new claims 207-212 and 215, are rejected under 35 U.S.C. § 103 as being unpatentable over Zhenghong et al. in view of Ono et al. for reasons made of record in Paper No. 8.

Zhenghong et al. teach antisense oligodeoxynucleotide phosphorothioates directed against the upstream region of the core gene initiation codon (#1893-1907), against the region upstream of the polymerase coding gene initiation region (#2297-

2313), and against the 3' region of 3.5 kb RNA for initiation of reverse transcription (#1817-1831) (see the abstract). Although these are not the exact boundaries of the targeted positions described by the Applicants for the oligos of the rejected claims, the oligos of Zhenghong et al. overlap those encompassed by the above claims.

Ono et al. teach the entire sequence of the HBV genome.

Since applicants only arguments concern the obviousness of an oligonucleotide that overlaps, encompasses or is included within the nucleotide sequence of another proven to have antisense activity, and this argument has been addressed above, a *prima facie* case of obviousness remains. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, knowing that the oligos taught by Zhenghong et al. inhibited HBV replication (as stated in the abstract), to use the sequence taught by Ono et al. to design other oligonucleotides that were complementary to the regions taught by Zhenghong et al. for the purpose of inhibiting HBV replication.

7. Claims 1-40, 44, 45, 48 and 49, and new claims 207-212, 215-220, 222 and 224, are rejected under 35 U.S.C. § 103 as being unpatentable over Bresser et al. in view of Ono et al. for reasons made of record in Paper No. 8.

Bresser et al. teaches an in situ hybridization assay which is useful for detection of specific DNA or RNA species within a cell. The oligos are designed for a specific target molecule based on a known sequence (column 16, line 26) and can be RNA or DNA (column 16, line 14). Multiple probes each modified with a unique label may be used simultaneously (Column 14, lines 59-63). Bresser et al. also teaches that the probes may be provided in the form of a kit (column 15, lines 32-35). Although Bresser teaches in situ hybridization using probes complementary to HIV, EBV and CMV (column 16, lines 44-46), Bresser et al. does not teach in situ hybridization with probes complementary to HBV.

Ono et al. teach the entire sequence of the HBV genome.

Applicants arguments do not address the rejection, since applicants argue that the combination of the references does not make obvious antisense oligonucleotides complementary to the HBV genome (page 16, last paragraph of Paper No. 10). A teaching of antisense technology relating to HBV was not set forth. The combination of the references does, however, render obvious any oligonucleotide designed from the HBV sequence, as disclosed by Ono et al., for the purpose of in situ hybridization of a viral genome, as taught by Bresser et al.

Since applicants have not addressed the rejection, a *prima facie* case of obviousness remains. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the sequence taught by Ono et al. to

design oligonucleotide probes for the detection and diagnosis of HBV using the in situ hybridization assay taught by Bresser et al.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bonnie Weiss whose telephone number is (703) 305-6775. The Examiner is available Monday through Thursday and every other Friday, from 8:00 to 5:30. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MINDY FLEISHER
SUPERVISORY PATENT EXAMINER
GROUP 1800

Bonnie D. Weiss, Ph.D.

November 26, 1996